Taxonomy of Immune Cells

Introduction

After finishing this course and rereading these notes, you'll realize how simple this lesson actually is. But approaching this topic for the first time can be challenging. That's because the traditional method for teaching this topic has been either by studying the lineage of cell lines and learning their intermediate stages, or by following a discussion on their histologic appearance. Neither is useful, as neither method explains what the cells do or how they do it. We loosely follow a semblance of cell-line lineage, and we'll mention histologic appearances, but we intend instead to break it down by cell function, using color and geographic location on the board (and in these notes) to act as an advanced organizer. If this feels uncomfortable, it's likely because it's different than how things are usually taught. This way is better.

Cell Lineage and an Overview

All cells of immunity (aka white blood cells, aka leukocytes) come from the **bone marrow**. Within the bone marrow there are cells called **pluripotent progenitor** cells. These cells are so undifferentiated that they can become any cell in the marrow. That includes leukocytes (white blood cells), erythrocytes (red blood cells), and platelets. Every time one of these cells divides, it retains a copy of its pluripotent self and produces a clone. That clone is partially differentiated but immature, resembling its pluripotent progenitor more than the cell it's destined to be. The clone is set on a path to complete differentiation, a mature cell. How the pluripotent progenitor does that, what the intermediary forms of the maturing clone are, and their histologic appearance, are simply not worth learning. There is much to learn, with many steps involved, and the yield is low. We will cover these details in Heme/Onc: General #3: *Hematopoiesis*.

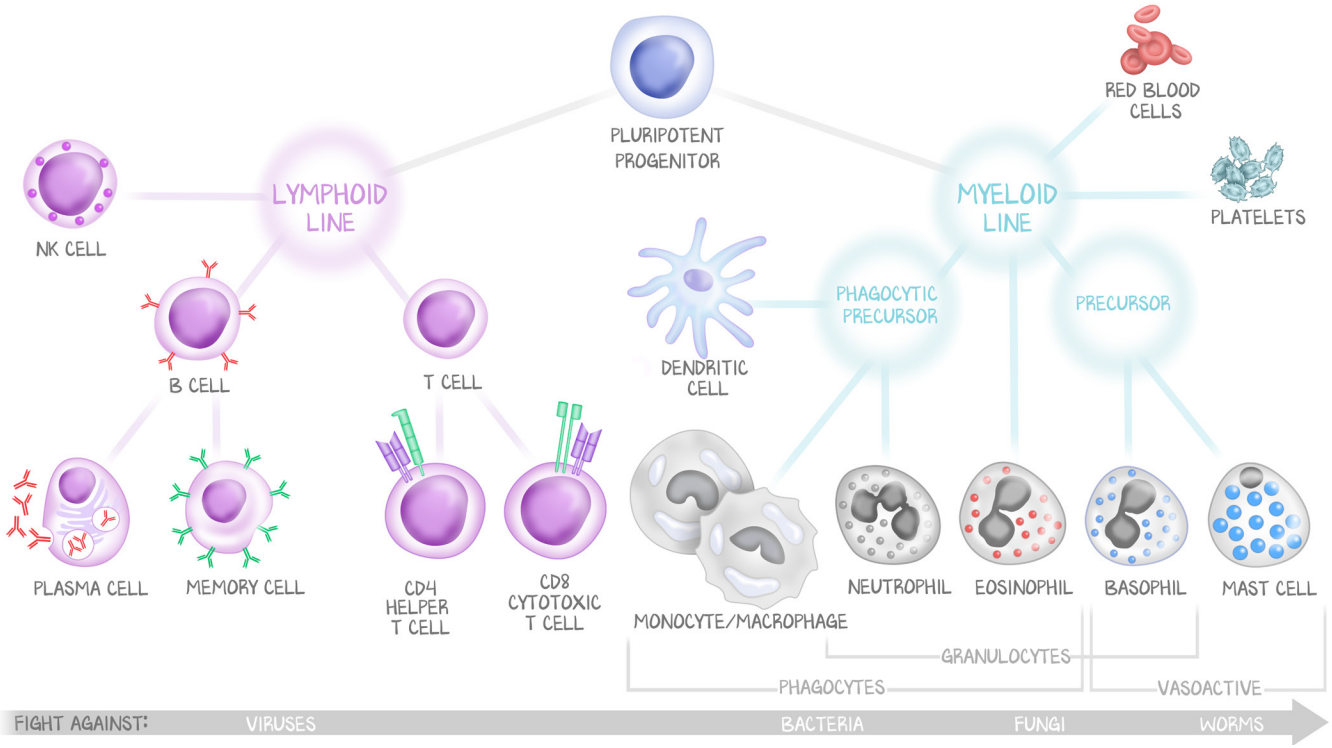


Figure 2.1: Cell Lineage
This image is complete, but downplays the cells we don't need, which will be discussed elsewhere in the Basic Sciences—RBCs, platelets, dendritic cells, and NK cells. The cells listed are the ones you need to know, their histologic appearance and their function. We group them this way to emphasize that lymphoid is (mostly) adaptive and myeloid is (mostly) innate immunity.

One lineage decision happens early and is quite relevant. That early undifferentiated stem cell divides and differentiates into either the lymphoid precursor lineage or the myeloid precursor lineage. The **lymphoid precursor** lineage can differentiate only into **lymphocytes** of the adaptive immune system (T cells and B cells) and NK cells (innate immune system lymphocytes). The **myeloid precursor** lineage can differentiate only into RBCs, platelets, and all the other cells of immunity.

Let's say that with more emphasis. Disregard NK cells. The **lymphoid precursor can make the cells of the adaptive immune system** while the **myeloid precursor can make the cells of the innate immune system.** Lymphoid, lymphocytes. Myeloid, everything else.

Now we must learn about the function and the histologic appearance of the final, differentiated cell lines.

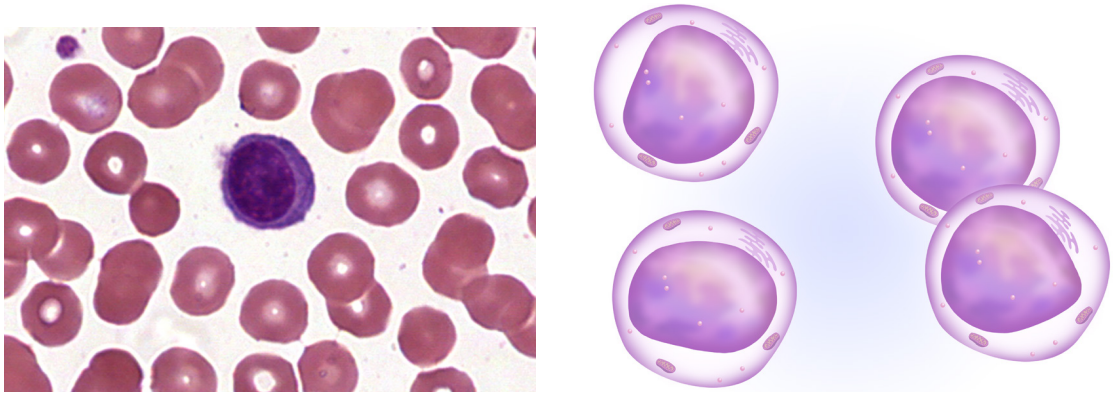
Lymphocytes

There are two main types of lymphocytes, B cells and T cells. B cells and T cells look similar to each other under microscopy, although their functions are very different and complex. They are the subject of about half of this immunology course. The goal of this lesson is to identify "a lymphocyte."

Mature **lymphocytes** are characterized by **very little cytoplasm** and are **mostly nucleus**. They stain **purple**, their nucleus being most of the cell. B cells and T cells can't be told apart by looking at them; instead, flow cytometry is needed to detect CD markers. CD markers in the single digits usually represent T cells (CD3 and CD4 or CD8), whereas CD markers in the double digits around 20 (CD19, CD20, and CD21) usually represent B cells.

T cells will be of two general varieties based on their function. **$CD4^+$ T-helper lymphocytes** connect the innate and adaptive immune systems. They help B cells proliferate when they find a bad antigen, and secrete cytokines to turn out a specific response against a specific pathogen. **$CD8^+$ cytotoxic lymphocytes** (CTL) are designed to kill cells, secreting cytokines to supercharge the innate immune system or, through apoptosis, eliminate an infected or cancerous self-cell.

B cells are all about immunoglobulins. B cells have immunoglobulins, which act as receptors, attached to their plasma membranes. They're antigen-identifying. When they identify an antigen, they internalize it, degrade it in a lysosome, and present it to T cells. **Mature naive B cells** and **memory B cells** use the immunoglobulin to detect antigens. That detection results in proliferation and differentiation into **plasma cells**, which secrete immunoglobulins as antibodies. Antibodies make the innate immune system better at doing its job by tagging antigens, making them targets for attack. You can't see immunoglobulin receptors or immunoglobulins.



(a) (b)

Figure 2.2: Lymphocytes
(a) A visualization of a lymphocyte on blood smear. (b) Artist's rendition of normal lymphocytes. Whether B or T cell is impossible to determine on light microscopy alone.

Myeloid Line

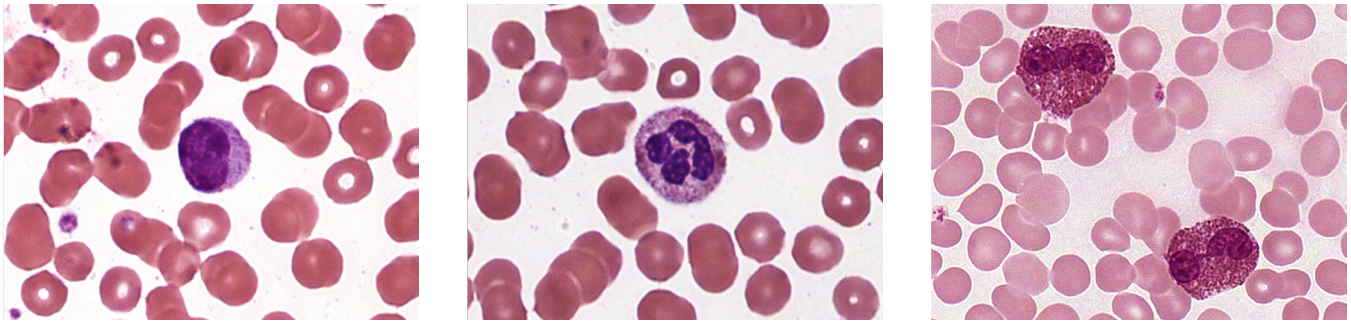
The only way to safely categorize the rest of the cells is as "not lymphocytes." Instead of lumping them together, we're going to talk about each of the different cell lines found in the myeloid line one at a time. Even though red blood cells and platelets are part of the myeloid cell line, they aren't immune cells, and won't be discussed here. Pay attention to the overlap that occurs in the myeloid line. There are different ways to categorize these cells. Most texts use the categorization under light microscope—what they look like. That does not help understand what they do or why, and invites tables of comparison that serve only to train the student to memorize them. That, in turn, invites error in recall. We approach them according to what they do, whom they fight, and how. We've also organized our whiteboard and introductory image in a way that acts as an advanced organizer. The order in which they are presented is best understood by looking at that image—we start with phagocytes, move into granulocyte phagocytes, then into vasoactive granulocytes (see Figure 2.1).

Phagocytes

A phagocyte is a member of the innate immune system whose job is to engulf and digest other cells. We will discuss in further detail the various types of phagocytes and their roles below. A **monocyte** and a **macrophage** are the **same cell**. What they are called depends on where they are in the body. Monocytes are macrophages in the blood; macrophages are monocytes in the tissue. Learn it that way; it makes things easier. They're **very large cells**, the largest of the immune system. These are the main **phagocytes** of the innate immune system. They have a **kidney-bean-shaped nucleus** and have **no granules**. However, because they are intensely phagocytic, when viewed under light microscopy they appear to have holes called **vacuoles—**remnants of their phagosomes—and lysosomes. They're rarely the first line of defense, but they're really good at phagocytosis. Macrophages are also APCs—innate cells that can go back to tell the secondary lymph node cells what they're fighting.

The **neutrophil** is also a **phagocyte**. It has a **multi-lobed nucleus** and also cytoplasmic granules. Therefore the neutrophil is also a granulocyte. Its function is **phagocytosis of extracellular pathogens**, just like the macrophage. Neutrophils arrive first, then signal for macrophages to come help fight the invader.

The **eosinophil** is also a **phagocyte**. It has a **bilobed nucleus** and also cytoplasmic granules. So, like the neutrophil, the eosinophil is both a phagocyte and a granulocyte. Its function is the **phagocytosis of fungi and small parasites**. The eosinophil is often tested against other granulocytes by its histologic appearance. Eosinophils **stain red**.



(a) (b) (c)

Figure 2.3: Phagocytic Cells
(a) The monocyte/macrophage is a large phagocyte with a kidney-shaped nucleus. (b) The neutrophil has a multi-lobed nucleus and colorless ("neutral") granules. (c) The eosinophil is also a phagocyte, targeting fungi and small parasites. It has a bilobed nucleus and red granules.

A Different Approach to Teaching Leukocytes

We are using this section to confront the expectation that you need to study granulocytes in comparison to each other. Traditional educational methods have you look at the clear one (neutrophil), the red one (eosinophil), and the blue one (basophil). That makes sense, doesn't it? Not if you want to understand the immune system. The way we have organized it helps comprehension, purposefully dividing up this content in a way that most people don't. The section above was about phagocytes. The section that follows is about cells that use vasoactive compounds. The function, not what the cell looks like, is what we focus on.

If you haven't noticed, I'll make something explicit (see image 2.1). We've organized this lesson visually, left to right. The NK cells were farthest left on the image along with CD8 cytotoxic T cells. Both NK cells and CD8 cytotoxic T cells fight against cancers and viruses, ways of killing dysfunctional self-cells. They do this via the release of cytokines. In other words, they fight small invaders with small chemicals. Next were the macrophage and neutrophil, who fight with phagocytosis. They eat bacteria. They fight invaders that are larger than viruses but are small enough to be eaten. Then there were the eosinophils, who also fight with phagocytosis, only they go after larger invaders like fungi and small parasites. As we've moved from left to right, the cells have been aligned in the order of increasing size of the pathogen they attack. It just so happens that there are granulocytes who are also phagocytes, AND ALSO granulocytes who release vasoactive compounds.

What happens when you have an invading organism too large to ingest by phagocytosis? Well, those pathogens still need to be dealt with somehow. And our immune system does that by flushing them out. Enter the cells that fight through vasoactive granules.

Vasoactive Granules

These are taught last, are on the right of the whiteboard image, and are discussed with an intervening paragraph on education technique not because the last section was so important, but rather to force you to mentally separate basophils and mast cells from everything else, associating them together based on their function and the organisms they are designed to fight. DON'T learn basophils in context of eosinophils. DON'T compare them.

Basophils are granulocytes but not phagocytes. **Basophils = Blue = Basic Staining = Acidic Granules.** Basophils **have granules**. They are **not phagocytes.** Their nuclei are multilobular. Basophils stain blue. Their granules, however, have nothing to do with killing cells or digesting their pieces. The **vasoactive granules** of basophils cause vasodilation and secretion of body fluids. Tapeworm too big for a cellular mechanism to kill it? Then let's flush it out.

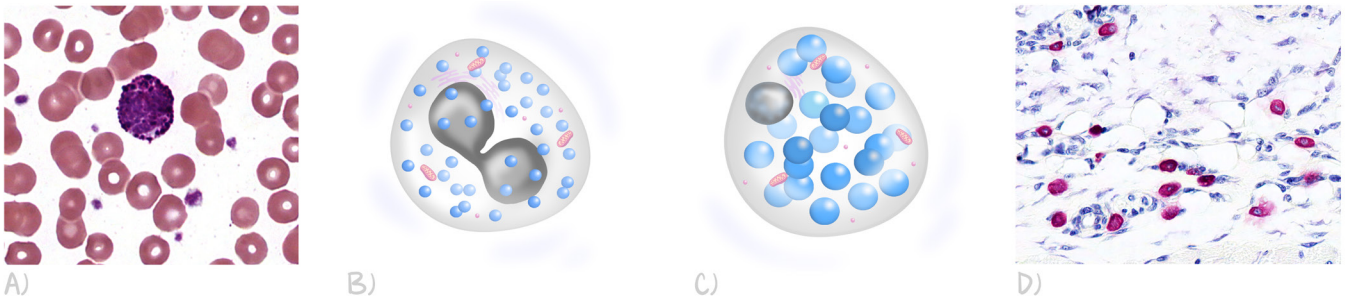


Figure 2.4: Cells with Vasoactive Granules
(a, b) The basophil has small blue granules. (c, d) The mast cell has HUGE blue granules. You should learn that these both release vasoactive compounds (like histamine) to expel larger parasites that can't be phagocytosed. However, where you will actually deal with them is mast-cell degranulation from crosslinking IgE, which causes allergies and asthma.

Some questions do get asked about an image on the slide. And for me, I had the worst time with the color of granules. So I learned only this, then extrapolated the rest: "Basophils are Blue because they stain Basic…and therefore their granules are acidic," and eosinophils are the opposite. The "stain B" is intentionally underlined. Say, "stain basic." Say, "Stain Bee Basic."

Mast cells are also granulocytes but not phagocytes. They also have blue vasoactive granules. Mast cells are often tested in the scenario of a slide—they're usually just a distractor for "something with granules that stains blue." But they look very different. Mast cells have a different nucleus shape than basophils and have **much larger granules.** The granules of mast cells are HUGE and few in number, whereas the basophils' are small and great in number.

Basophils and mast cells attack large organisms that can't be phagocytosed—these are instead expelled by excess bodily fluids flushing out large cavities. Basophils and mast cells facilitate this generation of fluids by releasing contents such as **histamine** that cause vasodilation and increased production of fluids and mucus wherever the large organism is (for example, diarrhea due to an intestinal parasite). Through the increase in bodily fluids, the organism is flushed out. Although histamine isn't the only substance released, it is one of the most commonly targeted substances in allergy, as it is a major contributor to the symptoms of anaphylaxis.

Clinical Correlate

You get a complete blood count (CBC) with differential (differential is the percentage of white cells). If there is an increase in the white blood cell count, there must be inflammation. At this point in your training, let's assume that means infection. If there were an increase in the percentage of neutrophils, what would you expect to be the infectious cause? Neutrophils phagocytose bacteria, so likely a bacterial infection. If a patient were infected by a fungus, which of the cell lines would likely be increased on the differential? Eosinophils. Do you know how the automated differential is done? Size and histologic appearance of white cells. And because T cells and B cells look very similar, the machine can only tell you that the lymphocyte count is elevated, which can be suggestive of a viral infection.

Citations

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